A link between ECM plasticity and synaptic morphological evolution

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Abstract

We made a link between Extra Cellular Matrix (ECM) plasticity and the morphological changes in synapses after synaptic excitation. A recent study by Zhang et al [6] showed that transmembrane voltage causes movement of the cell membrane. Here we will study the relation between the mechanical properties of collagen which is the major component of the ECM and synaptic morphological changes in relation with the theory of DO Hebb [1].

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I. INTRODUCTION

Hebb [1] suggested that the representation of an object implies the activity of all cortical cells activated by this stimulus. It is this group of neurons that Hebb called a cellular assembly. Hebb thought that all cells were related by reciprocal connections. Hebb suggested also that if the activity of this assembly of neurons had a sufficiently long duration, a consolidation of the information happened through a process which rendered these connections more efficient. The memory effect was obtained (always following Hebb) by this 'preferential path' (cellular assembly), i.e. if a part only of this preferential path was activated, the whole cellular assembly would be stimulated, giving place to a memory effect.

This memory effect is linked to synaptic plasticity, on one hand. Synaptic plasticity is linked to dynamic modulation of the postsynaptic membrane [2]. Moreover, long term enhancement of synaptic efficacy may lead to model learning and memory [3, 4]. Luscher et al. [2] observed clear shape changes in denditric spines of dissociated hippocampal cells [5]. Indeed, they saw that spines seemed to oscillate with a period of tens of seconds but did not seem to change their cross section.

Straightforwardly, a recent study [6] showed that for in vitro cells, transmembrane voltage modulates membrane tension and therefore causes movement. This study showed that the lateral displacement (perpendicular to the cell membrane) could be up to $9nm$ with a period of voltage pulses of $50ms$. We can make a parallel between this movement artificially created and oscillations of spines observed by Luscher et al [2]. The amplitude of the lateral movement of the neurons in vivo depends on the electro membrane potential of the neurons and therefore on ionic concentration in and out of the cell [6].

On another hand, Pizzo et al. [7] studied the relation between the mechanical properties of ECM and the shape of cells, depending on the density in collagen fibrils and the duration of growth of the cells. Another study [8] showed that transected axons in the lateral hypothalamus of mice could extend after the lesion if the deposition of type IV collagen and the formation of a fibrotic scar was prevented. A similar article [9] leaded to the same conclusion.

II. MODEL

The lateral movement due to transmembrane voltage modulations will create a strain on the collagen which surrounds the synapse (here we deal indifferently with the axons and the dendrites) [6].

In brain, the neurons are embedded in an extra cellular matrix which is essentially composed of type I collagen. This collagen matrix may be seen as isotropic: the collagen fibers have a random orientation. But what will happen if the neurons apply a strain on this collagen matrix due to their lateral displacement during transmembrane voltage modulations?

Therefore, a study by Feng et al. on the mechanical and rheological properties of collagen [11] deduced, from their experimental results, the following equation for stress strain response of collagen:

$$\sigma = E_e.\gamma^2/(\gamma^2 + b.\gamma + c) + (\eta/\gamma)\sum_{\gamma_0}^{\gamma} e^{-[t(\gamma)-t(\gamma')]/\lambda} d\gamma' \quad (1)$$

where σ is the stress, γ the strain, t the deformation time of collagen, η the sliding viscosity and λ the relaxation time of collagen. The first term of right hand side of equation (1) is a non linear elastic plastic term for collagen where E_e, b, c are constants. The study of Feng et al [11] show that under strain, collagen undergoes contraction and has a visco plastic behavior well described by equation (1) and in good agreement with experiments. If the strain tends to a high value the stress will tend straightforwardly to a constant. That is the plastic behavior of collagen. Unrecoverable strain in cyclic loading test on collagen resulted in cyclic creep [11]. We can make a comparison with cyclic loading and cyclic normal strain due to lateral cyclic movements of neurons during the propagation of an electro membrane potential.

Let us analyse the behavior of collagen next to the membrane or next to a synapse. For that we have to evaluate the values of σ, and therefore γ,t,η,λ and Ee, b, c. From literature t is equal to $1ms$ to $50ms$ [10], and λ is equal to $30min$ to $1h$ [11]. In order to obtain η and γ one has to make a dimensional analyzis of these two parameters. γ is a force applied by the membrane on the collagen, its dimensions are $kg.m.s^{-2}$. Therefore, in terms of characteristics of the collagen which mass is $24.10^{-23}kg$ for a cube of 1000 molecules of lysine (for type I collagen), which length is of the order of $10nm$ for 10 molecules of lysine and taking the characteristic time equal to the deformation time, we obtain $\gamma = 24.10^{-25}N$. With the same reasoning, η is a viscosity thus its dimensions are $kg.m^{-1}.s^{-1}$ and its value

is equal to $24.10^{-12} kg.m^{-1}.s^{-1}$.

In order to study the results obtained for values of $E_e, b, c = 1$, we obtained the stress σ following equation (1) approximatively equal to $10^{13} kg.m^{-1}.s^{-1}$ which i as sufficient value to have an effect on the geometry of the collagen or ECM near the dendrite or axone.

III. DISCUSSION

Now that preferential paths have been created in our simple model of brain, let us also model the memory effect. Ganguly-Fitzgerald et al [12] showed that for Drosophilia, exposure to enriched environments (i.e. exposure to rich sensorial environments) affects the number of synapses and the size of regions involved in information processing [13, 14]. In our model, the preferential paths in the extra cellular matrix are regions where there is a lower concentration of collagen close to the neuron. Therefore, it will be easier for two neurons to connect along these preferential paths by a simple steric effect. Indeed, if we suppose that the direction of growth of neurons (dendrites or axons) is simply leaded by the stiffness of the extracellular matrix, the connection of two neurons via one synapse will be more frequent on the preferential paths. Plus, during paradoxical sleep, neurons undergo random lateral vibrations due to random propagations of neuronal excitations. The memory of an event (e.g. sensorial) will be the creation of a preferential path plus the creation of new synapses on this preferential path.

Memory and intelligence are linked: intelligence is the ability to link two different events which have been put into memory. Once again, if paradoxical sleep corresponds to a random propagation of neuronal excitation, the possibility to link two different preferential paths is linked the locations of these preferential paths and on the intensity of neuronal excitation during sleep.

IV. CONCLUSION

To conclude, for young mammals, the water concentration of brain is larger and therefore the sliding viscosity η and the relaxation time t of collagen based extra cellular matrix will be smaller than for the corresponding adult mammals. Therefore the stress σ resulting from the lateral vibrations of neurons will be smaller (see equation (1)). This will lead to vanishing

preferential paths and this explains the lack of long term memory in young mammals.

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[1] D.O. Hebb *The Organization of Behavior: A Neuropsychological Theory* (Wiley, New York, 1949)

[2] C.Lüscher, R.A.Nicoll, R.C.Malenka and D.Muller, Nature Neuroscience, **3** (2000) 545

[3] T.V.P.Bliss and G.L. Collingridge, Nature **361** (1993) 31

[4] F.Engert and T.Bonhoeffer, Nature **399** (1999) 66

[5] M.Fischer, S.Kaech, D.Knutti and A.Matus, Neuron **20** (1998) 847

[6] P.C. Zhang, A.M.Keleshian and F.Sachs, Nature **413** (2001) 428

[7] A.M.Pizzo, K.Kokini, L.C.Vaughn, B.Z. Waisner and S.L. Voytik-Harbin, J. of Appl. Physiol. **98** (2005) 1909

[8] H.Kawano, H.P.Li, K.Sango, K.Kawamura and G.Raisman, J. of Neurosci. Res. **80** (2005) 191

[9] N.Klapka and H.W. Müller, J. of Neurotrauma **23** (2006) 422

[10] M.F.Bear, B.W. Connors, M.A. Paradiso, *Neuroscience: Exploring the Brain* Second Edition, (Lippincott Williams & Wilkins Eds. , Baltimore , USA, 2001)

[11] Z.Feng, M.Yamato, T.Akutsu, T.Nakamura, T.Okano and M.Umezu, Artif. Organs **27** (2003) 84

[12] I. Ganguly-Fitzgerald, J.Donlea and P.J.Shaw, Science **313** (2006) 177

[13] H. van Praag, G.Kempermann and F.H.Gage, Nat. Rev. Neurosci. **1** (2000) 191

[14] M.Heisenberg, M.Heusipp and C.Wanke, J. Neurosci. **15** (1995) 1951